UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,716	03/28/2002	Andrew R. Labarbera	91830/0476600	1627

7590 12/20/2005

Frost Brown Todd
2200 PNC Center
201 East Fifth Street
Cincinnati, OH 45202

EXAMINER	
MARVICH, MARIA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 12/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/018,716	LABARBERA ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-95* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 March 2002* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/28/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to a Response to a Restriction Requirement filed 11/2/04. Claims 1-95 are pending in this application.

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-30) in the reply filed on 11/2/04 is acknowledged. The traversal is on the ground(s) that Groups I-III share a common antisense oligonucleotide and therefore no undue burden would be placed upon the Examiner to search all three Groups.

This is not found persuasive because the instant application is a national stage application under 35 U.S.C. 371 and hence the restriction mailed 3/22/04 was executed under unity of invention principles as set forth in 37 CFR 1.475 and 1.499. Under PCT practice for Lack of Unity search burden is not the standard and hence applicants' argument that a search of Groups I-III are without search burden is moot. PCT rules teach that "Any international application must relate to one invention only or to a group of inventions so linked as to form a single general inventive concept (PCT Article 3(4)(iii) and 17(3)(a), PCT Rule 3.1, and 37 CFR 1.475)." Furthermore, under PCT practice, unity of invention shall be fulfilled only when there is a "special technical features" that defines a contribution that each of the claimed inventions, considered as a whole, makes over the prior art. In the instant case, the claims do not represent a contribution over the prior art as demonstrated by Kleisch et al and Slootstra and Roubos (see below). Therefore, the instant claims were found to comprise three separate inventions as set forth in the restriction mailed 3/22/04.

The requirement is still deemed proper and is therefore made FINAL. Claims 1-30 are under examination in this office action. Claims 31-91 have been withdrawn as being drawn to non-elected subject matter.

In the response filed 11/2/04, applicants have correctly indicated that that claims 1-30 should have been assigned to Group I and claims 39-64 should have been assigned to Group II. Hence, the restriction requirement mailed on 3/22/04 incorrectly included Groups 1-39 in Group I whereas Group I comprises claims 1-30.

Information Disclosure Statement

An IDS filed 3/28/02 has been identified and the documents considered. The signed and initialed PTO Form 1449 has been mailed with this action.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 USC 119 as follows:

The instant case is national stage application of the international application, PCT/US00/13488 filed 5/16/2000, which appears to claims benefit of provisional applications 60/136,489 filed 5/28/1999 and 60/158,612 filed October 8, 1999. The MPEP teaches "The later-filed application must contain a reference to the prior-filed application in the first sentence(s) of the specification or in an application data sheet, for a benefit claim under 35 U.S.C. 120, 121, or 365(c), and also for a benefit claim under 35 U.S.C. 119(e). Applicants must insert a specific reference to the earlier filed applications." Therefore, an application in

which the benefits of an earlier application are desired must contain a specific reference to the prior application in the first sentence of the specification or in the application data sheet (37 CFR 1.78(a) and (a) (5).

Specification

The specification comprises a sequence listing on pages 65-69 that do not start on a separate page. Subsequently, a "Sequence Listing " as required by §1.821(c) was submitted on paper. However, to be correct, the sequence listing on pages 65-69 must be deleted to avoid duplicate sequence listings.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in that the metes and bounds of "a nucleotide sequence of a follicle -stimulating hormone receptor" are unclear. A follicle-stimulating hormone receptor is a protein and does not have any nucleotide sequences associated with it. Therefore it is unclear what the source of the nucleotide sequence is.

Claims 2-14 and 22-24 are vague and indefinite in that the metes and bounds of "the antisense oligonucleotide(s)" are unclear. Claim 1 recites that the composition comprises at least

one antisense oligonucleotide. However, claims 2- 14, which depend from claim 1 and claims 22-24 that depend from claim 7 recite alternatively "the antisense oligonucleotides " and "the antisense oligonucleotide". It is unclear if for example, applicants are specifically limiting the claims to one or more than one by the respective designations or if the references are actually generically referring to one antisense oligonucleotide. Furthermore, claims 4 and 5 recite "antisense oligonucleotides" and yet depend from claims that recite "antisense oligonucleotide" and these claims therefore lack antecedent basis. Claim 6 recites "antisense oligonucleotide" and depends from a claim that recites "antisense oligonucleotides". Claims 4-6 therefore lacks antecedent basis

Claim 2 is vague and indefinite in that the metes and bounds of "alpha-anomeric forms of deoxyribonucleotides and ribonucleotides" are unclear. It is unclear if by recitation that the composition can be "alpha-anomeric forms of deoxyribonucleotides and ribonucleotides" the composition comprises a combination of alpha-anomeric oligonucleotides of deoxyribonucelosides **and** ribonucleosides or if the composition comprises alpha-anomeric forms of deoxyribonucleosides **or** alpha-anomeric forms of ribonucleosides.

Claim 3 is vague and indefinite in that the metes and bounds of "a stable duplex" are unclear. The antisense oligonucleotide is said to form a duplex with the FSHR gene. Genes are comprised of DNA, which are double-stranded. It is not clear how a duplex of the gene and composition will form and not a triplex. For purposes of art, the stable duplex of claim 3 will be considered as forming with a transcript of the FSHR gene and not directly with the gene.

Claim 3 recites the limitation "the FSHR gene" in claim 1. There is insufficient antecedent basis for this limitation in the claim as the claim as recited recites the protein and not

the gene. Note that claim 1 also requires that the abbreviation in parenthesis "(FSHR)" be inserted following the phrase "follicle-stimulating hormone receptor".

Claim 4 and 5 recite the limitation "the transcript" in claim 3. There is insufficient antecedent basis for this limitation in the claim.

Claim 4 and 5 are vague and indefinite in that the metes and bounds of "lying within about" are unclear. The portion of the transcript is "lying within about" 60 nucleotides of the translation initiation codon. By "lying within" it appears as if the portion must all be within the 60 nucleotide range or is it that the portion comprises any single nucleotide within this range.

Claims 15 and 16 are vague and indefinite in that the metes and bounds of "the internucleosidic linkage" are unclear. The antisense oligonucleotide of claim 7 comprises at least one nuclease resistant internucleosidic linkage. It is unclear if applicants are specifically limiting the claims to one internucleosidic linkage by recitation in the singular or if more than one linkage is tolerated and all internucleosidic linkages meet the limitations of the dependent claims. Furthermore, claim 15 recites that these linkages can be a variety of compounds. The compounds are listed alternatively in the singular and plural. It is unclear if applicants are also by designation to a singular or plural compound specifically limiting the linkages to one or more than one.

Claim 16 is vague and indefinite in that the metes and bounds of "the internucleosidic linkage is a phosphodiester linkage" is unclear. The specification teaches that phosphodiester linkages are unmodified and hence would not be expected to be nuclease resistant (see page 21, line 16-19). Therefore, it is unclear if applicants intend on reciting that the phosphodiester

linkage is modified to become nuclease resistant of if in fact the linkage recited in claim 16 is in some other way nuclease resistant. If not, the claim lacks antecedent basis.

Claim 28 recites the limitation "said composition being" in claim 20. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Kleisch et al (Molecular and Cellular Endocrinology, 1992, Vol 84, pages R45-R49; see entire document).

Kleisch et al teach a composition comprising at least one probe that is a ribonucleoside (cRNA) complementary to a nucleotide sequence corresponding to monkey FSHR (see e.g. abstract). Absent evidence to the contrary, the probe meets the limitations of the composition as recited in claims 1 and 2 as the probe is an oligonucleotide that binds to the FSHR transcript. The antisense oligonucleotide was designed to target the extracellular coding region of FSHR. The cRNA formed stable duplexes with FSHR transcript as demonstrated by *in situ* hybridization, which demonstrated specific binding as an indicator of stable complex formation (see e.g. figure 1-6, page R46, col 2, paragraph 3 and col 1, paragraph 3). Given the broad nature of "about" it can be considered that the cRNA binds within "about" 40-50 nucleotides of the translation initiation codon given its binding to the extracellular domain as recited in claims 3-5.

As recited in part in claims 7-11, the probe would be expected to be specific for the FSHR gene (transcript) in the ovarian granulosa cell of the human host as the cRNA probe was designed based on the sequence of the human FSHR (see e.g. page R46, col 1, paragraph 3). Furthermore, the cRNA sequences are 28 and 29 nucleotides long (see e.g. page R46, col 1, paragraph 3).

Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Slootstra and Roubos (BBRC, 1991, Vol 179 (1), pages 266-171; see entire document).

Slootstra and Roubos teach a composition comprising at least one antisense oligonucleotide that is a ribonucleosides complementary to a nucleotide sequence corresponding to a region overlapping the translation start codon (see e.g. figure 1) as recited in claims 1 and 2.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-12, 14-22 and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kleisch et al (Molecular and Cellular Endocrinology, 1992, Vol 84, pages R45-R49; see entire document) in view of Bennett and Cowsert (Biochimica et Biophysica Acta, 1999, pages

19-30; see entered document) and Baracchini et al (US 5,801,154;see entire document) and in view of Gromoll et al (Genomics, 1996, Vol 35, pages 308-311; see entire document).

Applicants claim a composition comprises an antisense oligonucleotide that is capable of forming a stable duplex with a portion of FSHR transcript including the translation initiation codon and includes a pharmaceutical carrier or is in the form of a pill or liquid. Furthermore, the oligonucleotide is a phosphorothioated 18-mer antisense oligonucleotide with at least one nuclease resistant internucleosidic linkage.

The teachings of Kleisch et al are described above and are applied as before except;

Kleisch et al do no teach that the composition comprises an antisense oligonucleotide that is capable of forming a stable duplex with a portion of FSHR transcript including the translation initiation codon. Kleisch et al do not teach that the composition comprising the oligonucleotide includes a pharmaceutical carrier or is in the form of a pill or liquid. Kleisch et al do not teach that the oligonucleotide is a phosphorothioated 18-mer antisense oligonucleotide with at least one nuclease resistant internucleosidic linkage.

Bennett and Cowsert teach that antisense oligonucleotides provide ideal technology for analysis of gene functionalization and target validation in which nucleic acid sequence information is used to design inhibitors (see e.g. page 20, col 2, paragraph 3). The method is rapid and straightforward and requires only knowledge of a part of a target sequence (cDNA or genomic) (see e.g. page 22, col 2, paragraph 3). As well, Bennett and Cowsert teach that the *in vivo* pharmacokinetic and toxicological properties of phosphorothioate antisense oligonucleotides are well-characterized (see e.g. page 23, col 2, paragraph 2).

Baracchini et al teach that a well known method of modulating genes is use of antisense oligonucleotides that are designed to specifically hybridize with nucleic acids by binding directly to mRNA or a selected DNA portion. Specifically, Baracchini et al teach that a target gene is identified preferably one that is a gene whose function is to be modulated and a target site is determined with in the gene. A preferred target site is the translation initiation codon because this is an effective region for modulation (see e.g. col 9, line 6-51). For specific hybridization, a "sufficient degree of complementarity is required to avoid non-specific binding but the oligonucleotide need not be 100% complementary to be specific" (see e.g. col 3, line 14-38). The oligonucleotides may be formulated in a pharmaceutical composition such as containing buffers or surfactants and may be administered as a capsules or liquid for oral administration or nasal administration or for intravenous drip or intramuscular administration (see e.g. col 4, line 23-64). Preferably the oligonucleotide is between 12 and 25 nucleotides, which encompasses an oligonucleotide that is an 18 mer. Furthermore, the linkages are modified for nuclease resistance such as by inclusion of phosphorothioate linkages. As well the linkage can include phosphodiester linkages even though these need not be nuclease resistant (see e.g. col 6, line 25-57). Furthermore, the oligonucleotides can be incorporated into liposomes (see e.g. col 4, line 26-30).

Gromoll et al teach that the sequence of the human FSHR receptor is well known in the art (see e.g. page 308, col 2, paragraph 3 through page 309, col 1, paragraph 3). Gromoll et al teaches that FSHR plays a crucial role in human reproductive physiology and that knowledge of the genomic structure and organization is a basis for investigation into pathological alterations of

the receptor and as a possible candidate in the area of reproductive failure (see e.g. page 310, col 2, paragraph 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to generate antisense oligonucleotides using the teachings of Bennett and Cowsert, Baracchini et al and Gromoll et al against FSHR as taught by Kleisch et al because Kleisch et al teach that it is within the ordinary skill of the art to generate and target the FSHR transcript the sequences of which Gromoll et al demonstrates is well known and essential for human reproductive physiology and because Baracchini et al and Bennett and Cowsert teach that it is within the ordinary skill of the art to design an antisense oligonucleotide such as a phosphorothioated 18-mer with at least one nuclease resistant internucleosidic linkage that is capable of forming a stable duplex with a portion of a transcript including the translation initiation codon and that includes a pharmaceutical carrier or is in the form of a pill or liquid. One would have been motivated to do so in order to receive the expected benefit of analysis of human reproductive physiology pathological alterations of the FSH receptor or to inhibit spermatogenesis or follicular development or to analyze reproductive failure (see Gromoll et al page 308, col 1 and page 308, col 2, paragraph 2). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 1-12 and 14-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kleisch et al (Molecular and Cellular Endocrinology, 1992, Vol 84, pages R45-R49; see entire document) in view of Bennett and Cowsert (Biochimica et Biophysica Acta, 1999, pages 19-30;

see entire document) and Baracchini et al (US 5,801,154; see entire document) and in view of Gromoll et al (Genomics, 1996, Vol 35, pages 308-311; see entire document) further in view of Baer et al (WO 91/04753; see entire document) and Zupi (US 6,080,727; see entire document) and Liang et al (US 5,872,206; see entire document).

Applicants claim a composition comprising an antisense oligonucleotide that is capable of forming a stable duplex with a portion of an FSHR transcript including the translation initiation codon. The antisense oligonucleotide is conjugated to a ligand-binding molecule such as an antibody or poly(L-lysine) or that the composition is in a form of a biodegradable sustained release composition.

The teachings of Kleisch et al, Bennett and Cowsert, Baracchini et al and Gromoll et al are applied as before except;

The references do not teach that the composition comprising the oligonucleotide is in the form of a biodegradable-sustained release composition or that the oligonucleotide is conjugated to poly(L-lysine) or a ligand-binding molecule such as an antibody.

Baer et al teach that ligand binding molecules such as antibodies can be conjugated to antisense oligonucleotides to generate affinity for a specific cells for targeted delivery (see e.g. page 9, line 14-25).

Zupi teaches that antisense sequences can be delivered to cells by conjugation to poly(L-lysine) to increase cell penetration (see e.g. col 11, line 41-50).

Liang et al teach methods of delivery of molecules such as antisense for therapeutic purposes (see e.g. col 13, line 35-46). The molecules are provided as biodegradable sustained release compositions for intramuscular delivery.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to conjugate the antisense oligonucleotide taught by Kleisch et al in view of Bennett and Cowsert, Baracchini et al and Gromoll et al with the ligand binding molecule or poly(L-lysine) taught by Baer et al and Zupi because Kleisch et al in view of Bennett and Cowsert, Baracchini et al and Gromoll et al teach that it is within the ordinary skill of the art to generate antisense oligonucleotides for delivery and because Baer et al and Zupi teach that it is within the ordinary skill of the art to conjugate the oligonucleotides to ligand binding molecules and poly(L-lysine). It would have been obvious to one of ordinary skill in the art at the time the invention was made to formulate the antisense oligonucleotide taught by Kleisch et al in view of Bennett and Cowsert, Baracchini et al and Gromoll et al as a biodegradable sustained release composition as taught by Liang et al because Kleisch et al in view of Bennett and Cowsert, Baracchini et al and Gromoll et al teach that it is within the ordinary skill of the art to generate antisense oligonucleotides for intramuscular delivery and because Liang et al teach that it is within the ordinary skill of the art to formulate the oligonucleotides as biodegradable-sustained release compositions. One would have been motivated to do so in order to receive the expected benefit of targeted delivery to cells of choice with increased cell penetration and for intramuscular delivery in a biodegradable sustained release form. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Nguyen, PhD can be reached on (571)-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1633

December 10, 2005